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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/545,199	04/06/2000	David E. Lowery	28341/6227.1NCP	9014

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 11/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/545,199	LOWERY ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-24 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *7-24,31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 7-24 and 31 are pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/12/2004 has been entered.

Response to Arguments

3. Applicant's arguments with respect to claims 7-24 and 31 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 7-24, 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These claims read on mutations of the polynucleotide of SEQ ID NO: 4, or attenuated bacteria comprising such polynucleotides, and species homologs

thereof. However, the specification does not provide adequate written description to support either species homologs to SEQ ID NO: 4, or any mutation resulting in decreased activity of the protein. There is inadequate written description to support claims to attenuated bacteria that comprise species homologues of the disclosed polynucleotide.

With reference to species homologues of SEQ ID N0: 4, applicant has provided only two sequences representing homologues to the polynucleotide. See page 40 (Table 1, identifying SEQ ID NO: 3 or 4 as an atpG gene from P. multocida); page 48 (Table 2, identifying SEQ ID NO: 132 as an atpG gene from A pleuropneumoniae); and page 60, lines 19-22 (identifying SEQ ID NO: 3 as encoding the atpG protein, the encoded polypeptide of which is identified as SEQ ID NO: 4). Each of the three sequences comprises numerous variations both in the polynucleotide sequence, and in the sequence of the encoded proteins.

The applicant has not identified any common structural core which one skilled in the art could use to identify any genus of polynucleotides in the instantly claimed genus of attenuated bacteria of the Family Pasteurellaceae. In essence, the applicant is claiming such polynucleotide homologues only by their functionality or the lack thereof, that of encoding atpG proteins. More than a statement of biological function is required to satisfy the 112, first paragraph written description requirement for a genus of attenuated strains of Pasteurellaceae that comprise a genus of mutant DNA molecules. See e.g. Amgen Inc. v. Chuzai Pharmaceutical Co. Ltd., 18 U.S.P.Q.Zd 1016, 1027 (CAFC 1991); and Fiers v. Revel, 25 U.S.P.Q.Zd 1601, 1604-05 (CAFC 1993). ln Amgen v. Chuzai, the Court of Appeals for the Federal Circuit stated that "it is not sufficient to define (a DNA) solely by its principal biological property, e.g. encoding of human erythropoietin." Id. at 1021. Rather, what is necessary is that (the applicant)

provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims." Id. at 1027. In these statements, the court has expressly stated that a DNA molecule must be described by means of description other than by naming the encoded protein to satisfy the 112 written description requirement. More recently, the Federal Circuit again took this position. In the case University of California v. Eli Lilly and Co., 43 U.S.P.Q.2d 1398, at 1406 (1997), the court stated that defining a cDNA by its function 'tis only a definition of a useful result rather than a definition of what achieves that result." The court also stated that such a description "does not define any structural features commonly possessed by members of the genus (of claimed CDNAS) that distinguish them from others." Id. Thus, it is clear that identification of polynucleotide by naming the polypeptide it encodes is not sufficient. In the present case, the only description that the applicant has provided for species homologues of SEQ ID NO: 4 is that they must also encode atpG proteins and this requirement is derived from the specification rather than being explicit in the claims). Such a description is clearly insufficient to support the claimed genus. polynucleotide homologues only by their functionality, that of encoding atpG proteins. More than a statement of biological function is required to satisfy the 112 first paragraph written description requirement for a genus of DNA molecules. See e.g. Amgen Inc. v. Chuzai Pharmaceutical Co. Ltd., 18 U.S.P.Q.2d 1016, 1027 (CAFC 1991); and Fiers v. Revel, 25 U.S.P.Q.2d 1601, 1604-05 (CAFC 1993). In Amgen v. Chuzai, the Court of Appeals for the Federal Circuit stated that "it is not sufficient to define (a DNA) solely by its principal biological property, e.g. encoding of human erythropoietin." Id. at 1021. Rather, what is necessary is that (the applicant) provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims." Id. at

1027. In these statements, the court has expressly stated that a DNA molecule must be described by means of description other than by naming the encoded protein to satisfy the 35 USC 112 first paragraph written description requirement. More recently, the Federal Circuit again took this position. In the case University of California v. Eli Lillv and Co., 43 U.S.P.Q.Zd 1398, at 1406 (1997), the court stated that defining a CDNA by its function 'tis only a definition of a useful result rather than a definition of what achieves that result." The court also stated that such a description does not define any structural features commonly possessed by members of the genus (of claimed CDNAS) that distinguish them from others." ld. Thus, it is clear that identification of polynucleotide by naming the polypeptide it encodes is not sufficient. In the present case, the only description that the applicant has provided for species homologues of SEQ ID NO: 4 is that they must also encode atpG proteins and this requirement is derived from the specification rather than being explicit in the claims). Such a description is clearly insufficient to support the claimed genus. While it may be obvious to those in the art to make mutations in a gene or protein, to achieve an attenuated bacterium, once the molecule has been identified as necessary for the virulence of the bacterium, it is not immediately obvious to those in the art as to what mutations will be effective. See e.g., Bowie et a1., Science 247: 1306-13 10, page 1306. Bowie et al presents a discussion on the tolerance of proteins to substitutions in the residue sequence. Although the reference is a discussion of protein substitutions, as the present case is concerned with polynucleotides encoding such proteins, the teachings of the reference are equally applicable to the mutations of the claimed inventions. The reference states that that proteins generally accept a wide variety of substitutions in their residue sequence. However, it also states that some residues must not be substituted at all without loss of the proteins function. The

reference also states that the effects of such substitutions are, currently, highly unpredictable. This statement is supported; and shown to be likely relevant to mutations in atpG, by the teachings of Humbert et al. (J. Bacteliol. 17143): 1435-1444). This reference teaches that a particular mutation in this gene lead not to an attenuated bacterium, but to a bacterium with resistance to common antibiotics. Abstract. Thus, one skilled in the art would not be able to recognize from the current disclosure any substitutions, or other mutation (except, perhaps, deletion of the whole polynucleotide) that would result in a decreased gene product activity,

As stated above, the Federal Circuit has held that claiming polynucleotides disclosed by their biological function alone is inadequate to meet the written description requirements. In the present case, not only does the application claim additional undisclosed polynucleotides without such support, it further claims modifications to both the disclosed and undisclosed polynucleotides by the effect of such modifications.

3. Claims 7-24, 31are rejected under 35 U.S.C. 1 12, First paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are described above. The claims are rejected because the applicant has not provided sufficient disclosure in the application to enable one skilled in the art to make or use any mutants of any Pasteurellaceae atpG polynucleotide, or a bacterium comprising such, wherein the mutation results in a decreased activity of a gene product.

Just as the applicant has not provided sufficient written description support for these claims, the applicant has also not provided sufficient information for one skilled in the art to

make or use the claimed polynucleotides without undue experimentation. In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112, first paragraph, such that one skilled in the relevant art could make or use the invention without undue experimentation, the courts have put forth a series of factors that may be considered. See, In re Wands, 8 USPQZd 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 198$. These factors include the following: (1) the quantity of experimentation necessary (2) the amount of direction or guidance presented; (3) the presence or absence of working examples', (4) the nature of the invention', (5) the state of the prior art', (6) the relative skill of those in the art (7) the predictability or unpredictability of the art and (8) the breadth of the cairns. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, the applicant has neither provided any direction or guidance, nor any working examples in the specification as to any potential mutations of SEQ ID NO: 4 that would satisfy the limitations of the claims. However, the claims read on any mutation to that sequence, and to homologs thereto that have the effect of decreasing the activity of the gene product. Just as the breadth of the claims is great, so is the number of potential mutations that may be made. Not only are there numerous substitutions that may be made, but there are also large numbers of insertions and deletions that may be made in the polynucleotide sequence. Although the number of operative embodiments is also likely to be high, the lack of guidance leading to them tends to show that they are not readily identifiable. Thus, the factors of claim breadth, guidance, and quantity of experimentation tend to favor a finding of undue experimentation.

While those participating in the art of the relevant technology (genetic and protein

manipulation) are generally highly skilled, the art is also rife with complexity. See also, discussion above in the written description rejection (demonstrating the lack of obviousness as to what mutations may be operable absent guidance). Knowledge of the sequence of protein or polynucleotide alone is not sufficient for those skilled in the art to make any mutation to a molecule and have confidence as to the effects that such a mutation would have. See e.g., Bowie, supra. Although Bowie also points out that information gathered from groups of similar or related proteins often helps in making predictions as to the effects of particular mutations. Bowie, pages 1308-1309. However, while the applicant has provided a few related proteins in the specification, there is no discussion as to the structural relationships among them. Rather, the sequences are set out, and it is left to those in the art to run comparisons to determine what the similarities among them are, and to determine which of them are important and which are not. In short, that applicant has invited others in the art to determine what mutations would achieve the desired affect without providing them any guidance indicating what the potential operable embodiments are. Given the complexity of the art, the breadth of the claims, the number of potential mutations, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the specification to enable those skilled in the art to practice the claimed invention without undue experimentation.

4. Claims 7-24,31 are rejected under 35 U.S.C. 1 12, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These claims are rejected because the applicant has not described how a mutation in

the protein coding regions can result in decreased expression of the gene product nor identified any such mutation. While a mutation in the coding region may result in the production of truncate; inactive, more or less active proteins, or no protein at all, it is unclear how such a mutation can affect gene expression. Mutations effecting changes in gene expression are generally in the non-coding regions of a gene. The polynucleotide sequence disclosed for SEQ ID NO: 4 comprises only the coding region of the atpG gene.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 7-12, 14-18, 20-24, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Kooistra et al (1976).

Kooistra et al disclose the instantly claimed invention directed to an attenuated Pasteurellaceae bacteria comprising a functional mutation in an atpG gene (mutants deficient, see title), wherein the functional mutation (lack DNA dependent ATPase activity, see Figure 2, Table 4, page 34) attenuates(see Table 7, page 36) the bacteria (sensitive to mitomycin C, deoxycholate and streptomycin).

The Haemophilus influenzae strains of Kooistra et al belong to the instantly claimed genus of attenuated bacteria. The disclosed mutants are functional mutants that lack ATPase activity, which is indicative of a decrease in biological activity, expression and/or inactive

product being expressed. The disclosed Haemophilus strains therefore lack a functional F1FO-ATP synthase (ATPase) which comprises atpG. A non-functional ATPase indicates the presence of a functional mutation in the atpG. While the reference does not specifically mention atpG, the reference does disclose and describe a functional mutation that attenuates the bacteria which lacks ATPase activity (see abstract, and entire document), which in turn results in a functional mutation in the ATPase operon that comprises the gene for atpG. The mutant Haemophilus influenzae attenuated bacteria anticipate the instantly claimed functional mutant strains that evidence a functional mutation in the atpG gene.

Conclusion

1. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

2. Henderson (1998) is cited to show ATP synthetase gamma subunit to be a type of rotational component of a tiny motor.

3. Omote, H et al (1998) is cited to show F1Fo ATPase mutational analysis in E.coli.

4. Rahlfs et al (1999) is cited to show the F1F0 ATPase Operon from Acetobacterium woodii.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
November 08, 2004

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